Configurational Control in Stereochemically Pure Ligands and Metal Complexes for Asymmetric Catalysis**

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Dedicated to Professor José Barluenga on the occasion of his 60th birthday

Abstract: Enantioselective synthesis relies on suitable chiral mediators, which, in many cases, owe their stereochemical information to chiral ligands coordinated to metals. Like nature, which uses (diastereomerically pure) enzymes with several stereogenic centers to catalyze biological processes, chemists, for their purposes, tend more and more to turn their attention towards ligands and metal complexes with more than one stereogenic center or element of chirality. Selected issues of the resulting diastereomeric interactions as well as the advantages that result from the use of such complexes in catalysis are presented and discussed here.

Keywords: asymmetric catalysis · catalysts · chirality · ligand effects · metal complexes

Introduction

The asymmetric synthesis of enantiopure compounds is of primary importance in synthetic organic chemistry and, within this area, catalytic approaches are considered most favorable. Nature utilizes enzymes for this purpose and relies on configurational and conformational optimization by structural variation of homochiral building blocks.[1, 2] In "man-made" asymmetric catalysis, approaches involving metals are by far the most developed ones and in some cases equal enzymatic procedures with regard to selectivity and/or substrate scope.[3] Such metal catalysts usually consist of a metal center and a ligand bearing the stereochemical information in order to ensure the catalysis to proceed in a stereoselective manner.

In the early stages of ligand-induced multiplication of chirality, C_2 symmetry was believed to be most efficient;[4] this lead to an extensive use of ligands such as Kagan's DIOP and Noyori's BINAP (asymmetric hydrogenation), diols like tartrates (Sharpless epoxidation), BINOL and Seebach's TADDOL or nitrogen-based semicorrins introduced by Pfaltz.[5]

Subsequently, the synthesis of more complex ligand structures bearing different chelating groups has emerged and among them ligands with more than one element of chirality have become very popular. While the classification of diastereomeric interactions in stoichiometric asymmetric synthesis has already been developed and summarized in the seminal article by Masamune,[6] a detailed insight into the role of the various elements of chirality in asymmetric metal catalysis is still missing.

In this article we highlight some recent efforts on the structural characterization and elaboration of ligands and metal complexes with multiple stereogenic elements[7] and comment on the challenges and chances that arise from the use of such catalysts.
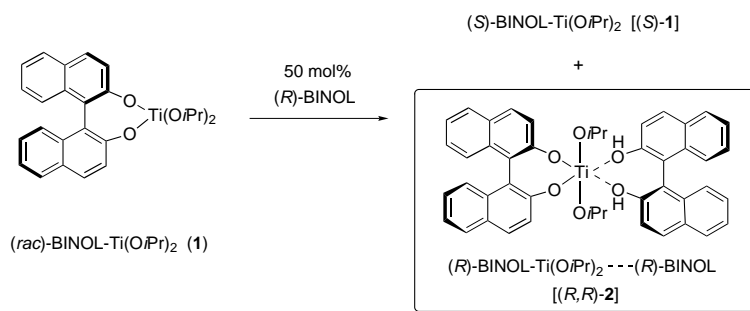
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Discussion

Diastereomeric interactions by combination of enantiomeric ligands: Several distinct approaches are known in this area. Within the scope of this article, non-linear effects[8] will be omitted, as will be the phenomenon of a partial, selective deactivation of a racemic catalyst precursor by an enantiopure additive (*chiral poisoning*).[9] The opposite strategy of the socalled *chiral activation*[10] consists of a stereoselective recognition of only one enantiomer of a racemic mixture by the optically active additive and is of more interest in this context, since as a consequence the generated catalyst is of diastereomeric composition. Along these lines, Mikami described an asymmetric Ti^{IV}-catalyzed carbonyl-ene reaction by activation

Scheme 1. Asymmetric activation of racemic Ti-BINOL complexes.[11]

of racemic Ti-BINOLate **1**.[11] Enantiomerically pure diols like (*R*)-BINOL were used as activators to give complex **2** (Scheme 1), as confirmed by independent NMR studies. It was then found that a given reaction in the presence of (*R,R*)-**2** was about 26 times faster than with (*R*)-**1**. Thus, the catalysis benefits from the in situ formation of a diastereomeric catalyst that has significantly higher activity than its single-enantiomer counterpart (*R*)-**1**.

A different but somehow related approach is the application of conformationally flexible ligands instead of racemic ones. Upon binding of such a compound to a metal complex that already bears an enantiopure ligand, the former adopts a preferential conformation that leads to a diastereomeric complex. Here, important contributions were made by Noyori and Mikami[12] and Reetz.[13] Reetz reported on the advantage of incorporating conformationally flexible biphenols into chiral diphosphites. When diphosphite **3a** bearing (*R*)-BINOL (Figure 1) was used in the Rh[I]-catalyzed hydrogenation
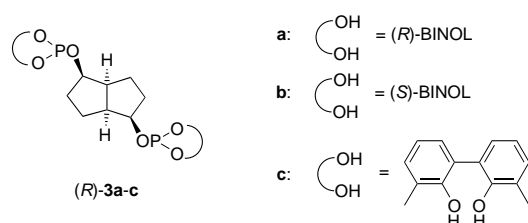

Figure 1. Diphosphite ligands **3a**–**c** incorporating an enantiopure bicyclic backbone and biaryls.[13]

of dimethyl itaconate, an *ee* of 95% was obtained for the saturated hydrocarbon. Ligand **3b** which results from the replacement of the (*R*)-BINOL group by its enantiomer (Figure 1) gave the product of opposite configuration in somewhat lower *ee* of 88%. Thus the transfer of the stereochemical information is dominated by the chiral binaphthyl and not the bicyclic backbone, and use of (*R*)-BINOL leads to the more effective combination. However, these results could even be improved when the enantiopure BINOL groups were replaced by conformationally flexible biphenols. Thus ligand **3c** (Figure 1) proved to be superior to **3a** affording the product with 98% *ee*. Given the fact that for **3c** the existence of three interconverting diastereomeric diphosphites is to be expected [(*R,R,R*), (*R,S,S*), (*R,R,S*)], from the observed high enantiomeric excess the authors concluded that the catalytic

process must have involved selective catalyst formation in situ. From the absolute (*R*) configuration of the product and by comparison with the reaction outcome in the presence of **3a**, it was deduced that the metal complex of kinetic preference had been the (*R,R,R*) diastereomer.

The flexibility of the coordination behavior of biaryls in ligand-to-metal binding has nicely been demonstrated by Gagné and co-workers.[14] They investigated platinum(II)-diphosphine complexes of type **4** (Figure 2) and found for **4a**, which contains dppe and axially chiral (*S*)-BINOL, a preferred λ-skew conformation of the
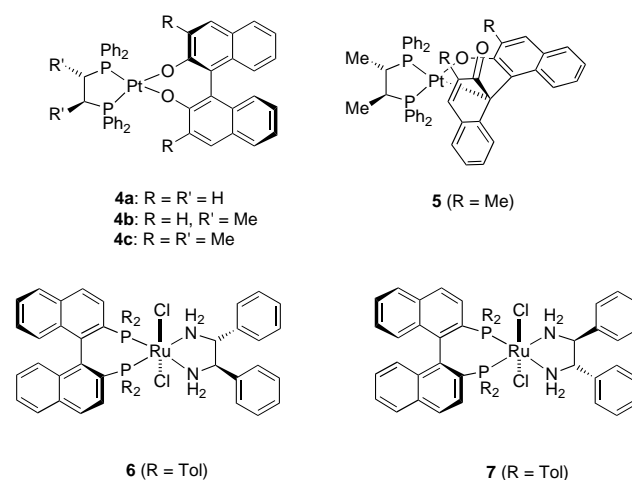

Figure 2. Isomeric Pt[II] complexes **4** and **5** bearing chiraphos and axially chiral binaphthols[14a,b] and diastereomeric Ru[II] complexes **6** and **7** as catalyst precursors for highly enantio- and diastereoselective ketone reductions.[15]

diphosphine ligand. Consequently, for chiraphos, which represents a chiral derivative of dppe, the existence of matched and mismatched cases was expected because its backbone substitution only allowed limited space for constitutional flexibility. Indeed, while a single defined solid-state structure was determined for the matched case [(*S*),(*S,S*)-**4b**], the constraint (*R*),(*S,S*)-**4b** (mismatched combination) revealed the existence of up to eight different conformational isomers in the elemental cell.[14a] In a subsequent elegant investigation, Gagné showed that such conformational strain must be limited; while the coordination of (*S*)-3,3′-dimethyl-BINOL and (*S,S*)-chiraphos to a Pt[II] center leads to a stereochemically preferred complex (*S*),(*S,S*)-**4c**, the corresponding mismatched complex is not obtained. Instead, the BINOL fragment is altered by a keto-enol dearomatization that results in the formation of complex **5**, which displays coordination through the α-carbon (Figure 2).[14b]

In 1995, Noyori introduced a novel asymmetric hydrogenation of ketones catalyzed by Ru[II]-BINAP-1,2-diamine complexes.[15] The combination of two chiral ligands was

essential to render the catalytic system highly enantioselective, and the use of enantiopure diamines guaranteed both excellent enantioselectivities and high chemoselectivities. Combinations in which the Ru-complex was formed from either an achiral bisphosphine or diamine resulted in much lower enantioselectivity.[15a] In an interesting study, a drastic synergistic effect for the complex derived from BINAP and DPEN was found in the reduction of (R)-carvone. While all four diastereomeric catalysts led to complete reduction, the diastereomeric ratios of the products were in the range of 100:0 to 34:66![15c] For this ruthenium-based system, the two diastereomers formed from the reaction of the polymeric ruthenium complex $[(\text{Tol-BINAP})\text{RuCl}_2(\text{dmf})_n]$ with DPEN were structurally characterized.[15d] In the reduction of 2,4,4-trimethyl cyclohexenone, (S)-(R,R)-**6** (Figure 2) proved to be a highly successful complex giving the correponding (R)-configured alcohol with 96% ee. Interestingly, the reduction of 2-methylacetophenone was most efficiently catalyzed with diastereomer (S)-(S,S)-**7** (Figure 2) to give the (R) product with 97.5% ee, while (S)-(R,R)-**6** led to the formation of a product with the same configuration, but much lower ee (8%).[16]

These results are of importance when it comes to a discussion of an apparently *unselective* chiral activation as described by Noyori and Mikami.[16] An attempted activation of racemic $[(\text{Tol-BINAP})\text{RuCl}_2(\text{dmf})_n]$ with enantiopure (S,S)-DPEN resulted in formation of an equal mixture of (S)-(S,S)-**7** and its (R)-(S,S) diastereomer [ent-**6**]. Control experiments revealed that the reaction equilibrium was far on the side of the mixed-ligand complex and that the complexation of the diamine was irreversible. Thus, enantiomeric excesses depend on the respective enantioselectivities and relative reaction rates of the two competing diastereomers. For example, reduction of 2,4,4-trimethyl cyclohexenone was accomplished with 95% ee, a value close to the 96% ee obtained with complex ent-**6** prepared from enantiopure (R)-Tol-BINAP and (S,S)-DPEN; this indicates that this complex dominates the catalysis largely over its diastereomeric counterpart.

As already indicated before, the same authors also investigated the incorporation of prochiral BIPHEP ligands in ruthenium diphosphine/DPEN complexes. In the presence of enantiopure diamines, the formation of unequal mixtures of diastereoisomers was observed by NMR spectroscopy. The superiority of the thereby generated ruthenium complexes over the corresponding ones generated from racemic BINAP ligands was shown by comparison of the respective enantioselectivities in asymmetric catalytic hydrogenations of ketones.[12]

Finally, from a preparative point of view the most convenient approach would consist of an in situ self-organisation of the catalyst in the presence of various potential chiral ligands. The general possibility of such a concept has been devised by Mikami.[17] For the most simple case of equal substoichiometric amounts of metal source and two different ligands, for example, for Ti(O-iPr)$_4$, (R)-BINOL, and (R)-5-Cl-BINOL, a smart self-assembly of all components was observed and an ee of 97% was obtained in an asymmetric catalytic carbonyl-ene reaction. Similar observations were made for other ligand

combinations including TADDOL and DIPT. In all cases, higher enantiomeric excesses were observed than for those reactions that only relied on a single enantiomeric ligand.

Given the fact that in asymmetric processes fine-tuning of the chiral mediators is of primary importance, the use of diastereomeric complexes derived from a combination of enantiomeric ligands, as presented here, represents a powerful conceptual approach. As described above, either careful optimization of stereochemical interactions or in situ self organization may thus lead to the finding of suitable chiral complexes. It is also important to note that for different substrate structures two diastereomers within a given set of catalysts can both be highly efficient.

Diastereomeric chiral-at-metal complexes: Interactions of chiral ligands with suitable metal precursors might also result in the formation of a stereogenic metal center (*chiral-at-metal complexes*).[18] Thorough investigation into the role of such a chiral metal center during the course of catalysis is often hampered by the fact that both diastereomers are not available in stereochemically homogeneous form. Instead, most often an epimeric mixture is obtained.

In a recent study, Carmona, Cativiela et al. showed that in the course of an asymmetric Diels–Alder reaction an epimerized ruthenium center was preserved even during the complexation step of the substrate.[19] However, an epimeric ratio of 82:18 was found to undergo a change to 90:10 during coordination of the dienophile; this makes a definite conclusion on the role of the stereogenic metal center in catalysis almost impossible. Furthermore, the degree of epimerization was shown to be highly solvent dependent. Related observations have been reported by Brunner for asymmetric isomerisation processes in the presence of diastereomeric mixtures of ruthenium complexes.[20]

By far the best investigated system is based on the ruthenium-diamine complexes **8**–**10** as described by Noyori and co-workers (Scheme 2).[21] Two facts on these catalysts for
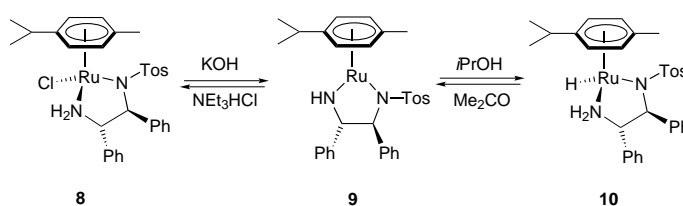
Scheme 2. Diastereomeric chiral-at-metal complexes **8** and **10** and intermediate **9** for asymmetric transfer hydrogenation.[21]

asymmetric transfer hydrogenations of ketones are especially noteworthy. First, formation of only one diastereomeric catalyst precursor **8** was observed, and, more importantly, formation of the catalytically active species **10** takes place in a completely stereospecific manner via intermediate **9**. In this sequence all steps are reversible, and it can therefore be considered as a rare example of a constant regeneration of metal stereocenters[22] in diastereomeric complexes. Furthermore, the present example is unique in that for this chiral

catalyst system all species involved, the catalyst precursor (**8**), an intermediate (**9**), and the active catalyst itself (**10**), have been fully characterized by solid-state structures. Since monotosylation of the diamine is crucial for high enantiose-lectivity the overall diastereomeric composition of the catalytic species cannot be altered.

Asymmetric catalysis with enantiomeric chiral-at-metal complexes is still unknown. Yet, compounds of diastereomeric configuration, in which the configuration of the chiral metal center is (pre-)determined by the attached chiral ligand, represent the only approach to generate suitable catalysts of this type.

Diastereomeric interactions in ligands with more than one element of chirality: In the large field of diastereomeric ligands, many examples are known in which the ligand structure is determined by a combination of stereogenic carbon centers. In most cases only one of such diastereomers acts as successful ligand, whereas the other leads to a much lower enantioselectivity. However, several exceptions have also been described. Certainly one of the most prominent examples in which two diastereomeric ligands lead to products of opposite absolute configuration with almost equal enantiomeric excess is the asymmetric dihydroxylation of olefins (AD) as developed by Sharpless.[23] Here, DHQD- and DHQ-based compounds like **11** and **12** act as chiral ligands (Figure 3). The AD of stilbene can serve as a representative

Figure 4. Metal complexes bearing ligands of diastereomeric composition. Mn[III] complex **13** and its diastereomer **14** for asymmetric oxidation reactions.[24] Diastereomeric binaphthyls **16** and **17** to be used as ligands in asymmetric Wacker type reaction and schematic representation of derived Pd complexes (**A** and **B**, binaphthyl ligand cores are omitted).[26]
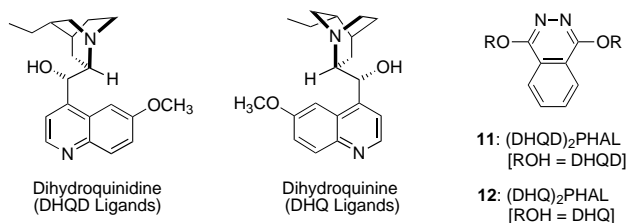

Figure 3. Pseudoenantiomeric alkaloid type ligands **11** and **12** for the asymmetric Sharpless dihydroxylation and aminohydroxylation of olefins.[23]

example; under standard conditions in the presence of (DHQD)$_2$PHAL **11** the corresponding (*R,R*)-configured diol is obtained with 99.5% *ee*. Use of (DHQ)$_2$PHAL as ligand results in the formation of the (*S,S*) enantiomer with identical *ee*; this confirms that **11** and **12** act indeed as pseudo-enantiomers. The same reaction behavior was later trans-ferred successfully to the related asymmetric aminohydrox-ylation.[23c,d]

However, diastereomeric ligands that act as pseudo-enan-tiomers are relatively scarce. In almost all cases, a noticable difference in catalytic behavior is found and, from the stereochemical point of view, both diastereomers commonly lead to drastically different selectivities.

In the area of diastereomeric ligands that combine different stereogenic carbon centers, much work has been done by Katsuki. Chiral manganese-salen complexes like **13** and **14** (Figure 4), which originally were developed for the asymmet-ric epoxidation of unactivated olefins, have found further
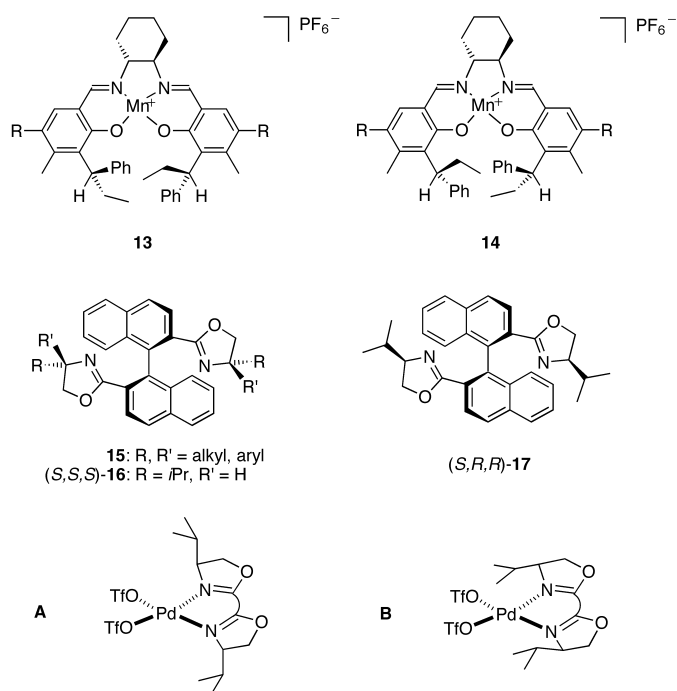
application in other metal-catalyzed processes.[24] However, the fact that the catalysts' preferential stereochemical com-position differs from substrate to substrate deserves special attention. Although drastic differences in asymmetric induc-tion as observed for olefin and sulfide oxidation could be explained on the basis of the respective configurations (sp^2 hybridization in the case of the olefin, sp^3 for the sulfide), this again underlines the importance of gaining insight into the catalysts diastereomeric nature to ensure optimum sub-strate–catalyst interactions. In recent work, the design of second-generation salen ligands that combine elements of central and axial chirality was reported, and detailed X-ray structure analyses of these complexes have been applied to rationalize the different substrate specifities that again were found for several reactions.[25] Careful exploration of these data also allowed the determination of the crucial role of a donor additive, which in some catalytic oxidation reactions had been found to be of primary importance for only one of the diastereomers.[25b]

Another well-studied ligand system that displays both axial and central chirality has been explored by Hayashi.[26] Originally introduced for asymmetric cyclopropanation reac-tions,[26a] ligands of type **15** (Figure 4) have gained interest owing to their successful application in elegant asymmetric Wacker-type cyclizations,[26b–d] for which a strong dependence of the product *ee* on the relative configurations of the elements of chirality was observed. For a cyclization in the presence of (*S,S,S*)-**16** (Figure 4) reasonably high conversion was achieved and the product had an enantiomeric excess of 96%. Use of diastereomeric (*S,R,R*)-**17** (Figure 4) resulted in

very low conversion and enantioselectivity as well as formation of the product with opposite absolute configuration. These results were rationalized by inspection of the X-ray structure of (S,S,S)-[**16** · Pd(OCOCF₃)₂].[26c] With regard to the square-planar coordination around the central palladium atom, an almost perpendicular orientation of the isopropyl groups was observed for this complex (Figure 4 structure **A**) which could also be verified for the solution structure. A model structure for (S,R,R)-[**17** · Pd(OCOCF₃)₂] revealed a situation in which these two isopropyl substituents were nearly parallel to the coordination plane (Figure 4 structure **B**). This result suggested that enantioselectivity, and rate and face selectivity are highly dependent on the relative orientation between the isopropyl substituents of the oxazoline moieties and the coordination sphere of the central palladium atom. Unfortunately, these results could not be generalized to a rational catalyst design and when attention was turned to a different type of substrate, a major ligand optimization turned out to be necessary.[26d]

At present, the most comprehensive investigations on the influence of stereochemically homogeneous ligands containing different elements of chirality come from the field of ferrocene chemistry. The first investigation of such type has been undertaken by Hayashi, Kumada, and co-workers who studied the influence of planar chirality in asymmetric Grignard cross-couplings.[27] In the Ni^II-catalyzed reaction between α-phenylethylzinc chloride and vinylbromide in the presence of the P,N-chelating ferrocene **18** (Figure 5), the (S)-configured coupling product was obtained with 68% ee. Diastereomeric ferrocene **19** led to the formation of the opposite enantiomer with 54% ee. Apparently, changing the absolute planar chirality of the ligand results in a reverse absolute configuration of the product, while the extent of enantioselectivity is almost identical. Finally, catalysis in the presence of ligand **20**, which omits the central chirality of **18**, affords a product with 65% ee and (S) configuration. Consequently, the conclusion was drawn that mainly the planar chirality was decisive for the stereochemical course of the reaction.

It took until the late 1980s before the impact of planar chirality in diastereomeric ferrocenes was investigated again. From studies with diastereomers **21** and **22** (Figure 5) Pastor and Togni concluded that in Ito's asymmetric gold(ı)-catalyzed aldol-type reaction the decisive stereochemical information also depended on the stereogenic center in the side chain. Consequently, they introduced the so-called *principle of chiral cooperativity* representing Masamune's matched/mismatched cases for internal stereoelements.[28a,b] Moreover, with the knowledge of the preferred diastereomeric ligand configuration, the catalysis turned out to be merely unaffected by the incorporation of further stereogenic carbon centers even when introduced in racemic form.[28c]

Later concise investigations include ferrocenyl oxazoline ligands for diethylzinc additions to aldehydes as described by us[29] and Tsuji–Trost alkylations as reported by Dai.[30] In case of the hydroxyl oxazolines we found drastically different performances of ferrocenes **23** and **24** (Figure 5), which are diastereomers owing to opposite planar chirality (e.g., in the addition of ZnEt₂ to benzaldehyde: 93 vs 35% ee). Use of
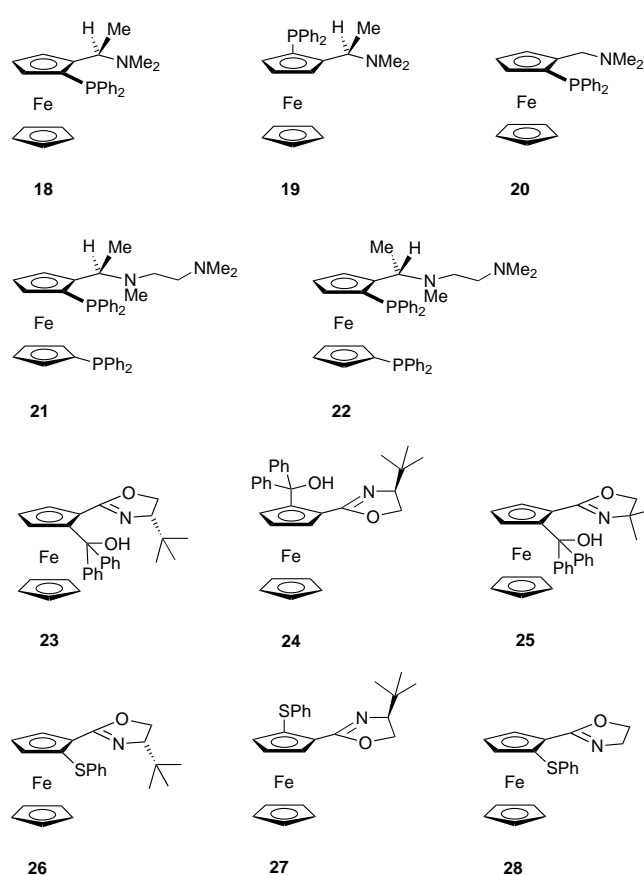

Figure 5. Representative planar chiral ferrocenes used in asymmetric catalysis: Grignard cross-coupling (**18–20**)[27], aldol-type cyclization (**21**, **22**)[28], dialkylzinc additions to aldehydes (**23–25**)[29], and Tsuji–Trost alkylation (**26–28**).[30]

ferrocene **25** that has a ligand with planar chirality only resulted in a comparably moderate enantioselectivity of 51% ee. We thus proposed that the right combination of the two stereoelements and their mutual interactions were of major importance for achieving high enantioselectivities. On the basis of the solid state structures of compounds **23** and **24**, we further concluded that the pseudo-C₂-symmetrical arrangement of **23** contributed to its high catalytic efficiency.[29b] In contrast, in palladium-catalyzed asymmetric Tsuji–Trost alkylations Dai found a nearly identical behavior of diastereomers **26** and **27**, whereas catalysis in the presence of ferrocene **28** with merely planar-chiral ligand afforded a product with a significantly lower enantiomeric excess (Figure 5). As a result, the stereogenic carbon center at the oxazoline ring was held responsible for the enantioselectivity.[30]

Thus, in the four afore-mentioned investigations four conclusions were drawn regarding the interactions of the elements of chirality: i) the sole importance of planar chirality, ii) the importance of central chirality introducing the concept of chiral cooperativity, iii) the importance of a preferential catalyst conformation, and iv) the sole importance of central chirality. It should be noted that currently no predictions can be made on the role and relative importance of the stereoelements involved and that any conclusion will not necessarily be valid for another series of ligands. This can

be convincingly observed from the relative catalytic performances of the pairs **23/24** and **26/27** derived from ferrocenyl oxazoline compounds. Albeit quite similar in structure on first view, their respective catalytic performances are significantly different!

In another approach, Helmchen and co-workers recently introduced cymantrene derivative **29** (Figure 6).[31] This compound results from the structural optimization of the original

29 (R = 2-Biphenylyl)   **30**

Figure 6. Cymantrene derivative **29** containing three elements of chirality as an improved structural development of **30**.[31]

enantiomeric diphenylphosphinooxazoline **30**, which by careful introduction of additional elements of chirality (a stereogenic center at phosphorus and planar chirality) increased the originally low enantiomeric excess to up to 99.9% *ee* in Pd-catalyzed asymmetric allylic substitutions on cyclic substrates.

The catalyses described so far make use of isolated diastereomerically pure compounds that were seperately synthesized and tested as potential ligands in asymmetric catalysis. However, at this point it should be noted that in some reactions even mixtures of diastereomers can be successfully employed. We have recently been able to devise an application in which mixtures of diastereomeric ferrocenes were used in asymmetric alkylations and arylations of aldehydes to afford products with >90% *ee*.[32] For example, dimethylzinc addition to benzaldehyde gave 95% *ee* upon use of a 1:1 mixture of **23** and **24** (Scheme 3), a result close to the
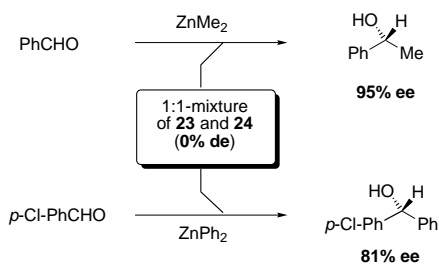
Scheme 3. Enantioselective alkyl and aryl transfer in the presence of a 1:1 mixture of diastereomeric ferrocenes **23** and **24**.[32]

97% *ee* obtained with diastereomerically pure **23**. Thus, expressing it differently, in this experiment an enantiomeric excess of 95% was achieved with a catalyst that had 0% *de*! Similarly, in the presence of 10 mol% of a ligand with 0% de, the diphenylzinc addition to *p*-chlorobenzaldehyde gave a product of 81% *ee*, which is comparable to the 82% *ee* obtained in the sole presence of **23**. These surprising results are explained by the drastically different reaction rates of the two diastereomers **23** and **24** under the reaction conditions. Only one of the ferrocenes, namely **23**, contributes signifi-

cantly to the catalysis that affords the corresponding product with high *ee*. In a sense, these results are related to those observed by Noyori and Mikami in the asymmetric ketone reduction for which they used a mixture of diastereomeric Ru[II] complexes derived from racemic Tol-BINAP and enantiopure diamine ligands as described above.[16]

Similar conclusions were drawn by Blackmond, Reetz, and co-workers in a recent contribution underlining the importance of kinetic evidence on mechanistic studies.[33] By employing a 1:1 mixture of Rh[I]-catalysts bearing diastereomeric diphosphites **3a** and **3b** in the hydrogenation of dimethyl itaconate the corresponding product with 55% *ee* was obtained. Apparently, one catalyst dominates the stereochemical outcome, and this fact again was explained by the difference in rate of the two catalysts that participate in the reaction.

As already pointed out before, an improved understanding of the interactions in diastereomeric ligands is of primary importance for the a successful application of such catalytic systems. The screening of enantiomeric ligand combinations might be time-consuming, but the search for an appropriate ligand with multiple stereogenic elements is even more difficult because it often requires a multi-step synthesis. Therefore one major target should be to achieve the desired structural modification within a reasonable period of time and by certain preparative ease. Given the various building units for potential future ligands with multiple stereogenic elements, it remains surprising that there is only a very limited number of reports on the screening of such structures by employing combinatorial chemistry. Within the several reports on the combinatorial development of chiral ligands for asymmetric transformations,[34] there is only one that specially includes the screening of stereochemically pure diastereomers.[35]

In summary, we have described representative examples of the use of structurally well-defined chiral metal complexes with multiple stereogenic elements in asymmetric catalysis. The combination of different enantiopure ligands seems to be well understood and has found several convincing applications. On the other hand, the use of stereochemically defined chiral-at-metal complexes as a whole and the role of the stereogenic metal itself remain a target for future investigations. In the steadily increasing field of ligands bearing more than one element of chirality, a routine elucidation of diastereomeric interactions and their consequences for the subsequent catalytic performance still constitutes an exception. It is to be hopeed that more careful attention will be paid toward this issue, especially in view of the growing number of new chiral ligands that are reported these days. By no means can one talk of a general way of *designing* ligands with multiple stereogenic elements, since there are no generally applicable routes toward a prediction of the resulting steric and stereochemical interactions yet. Therefore, a major task is to elaborate techniques for reliable prediction of general lead structures.[6, 36] These techniques might then finally allow us to deduce those rules that are required for a general ligand design.

Given the already high number of successful applications, we are convinced that predetermined diastereomeric interactions will continue to play an important role in the field of defined chiral metal catalysts and also will be crucial for the discovery of new efficient asymmetric processes.[37]

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